UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

KM

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/336,103	06/18/99	DOWNS K	960296.95912

HM12/1221

JEAN C BAKER
QUARLES & BRADY LLP
411 EAST WISCONSIN AVENUE
SUITE 2550
MILWAUKEE WI 53202-4497

EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	6

DATE MAILED: 12/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/336,103	DOWNS, KAREN M.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Group V, claims 21-23, in Paper No. 5 filed 10-10-00 is acknowledged.

Claims 1-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5 filed 10-10-00.

Priority

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 21-23 of this application. Application 08/838,384 does not provide support for obtaining mesenchymal cells that express a "specific test gene product", forming transgenic allantois using such cells and observing the effect of the "test gene product" on vasculogenesis as claimed. Therefore, the effective filing date of the instant invention is the filing date of provisional application 60/118,764 which is 2-5-99.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: A method of evaluating the effect of a transgene on vasculogenesis.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic allantois comprising a nucleic acid comprising a gene encoding a protein operatively linked to a promoter such that the allantois functionally expresses the protein to detectable levels, transplanting the transgenic allantois into an allantois of a histocompatible host, and observing the vascularization of the allantois in the host using methods known in the art, does not reasonably provide enablement for determining whether a "test gene product" is "beneficial" or "detrimental", forming a transgenic allantois using histoincompatible tissues or evaluating the effect of any "test gene product" on vasculogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For enablement purposes, mesenchymal cells are considered any cell that is part of the embryonic mesoderm which can become connective tissue, bone, cartilage, the circulatory system or the lymphatic system (www.dictionary.com, enter "mesenchymal"). A "transgenic allantois" is considered an allantois that contains transfected cells or an allantois isolated from a transgenic animal wherein the transgene is expressed in the allantois.

The state of the art at the time of filing was that mesenchymal cells transfected with a vector encoding a protein were transplanted into histocompatible allantois such that the effect of the expressed protein expression on vasculogenesis was observed (see Ribatti in 102(b) rejection below; page 456, col. 1, 7 lines from the bottom; col. 2, line 9; page 457, col. 1, line 5; page 459, col. 2, last paragraph through page 460, col. 2, line 5). In addition, allantois expressing lacZ isolated from transgenic mice had been transplanted into a histocompatible host allantois wherein the fate of the transgenic cells and the vasculogenesis in the host allantois was observed (see Downs in 102(b) rejection below; page 2770, col. 1, 2 lines from the bottom; col. 2, 1st and 2nd full paragraphs; page 2774, col. 2, line 6 and last line; page 2779, "Umbilical vasculogenesis").

The specification teaches isolating allantois explants and transfecting the explants *in vitro* with a vector encoding LacZ or GFP as well as isolating allantois explants from transgenic mice expressing LacZ. The transfected/transgenic explants are transplanted into the allantois of an embryo in a histocompatible host. The location and developmental fate of the transplant is determined by detecting marker gene expression and by cell surface marker expression throughout gestation of the embryo. The specification does not teach evaluating vasculogenesis using LacZ or GFP expression; however, such methods were known in the art (see Downs in 102(b)).

The specification also discusses using allantois explants transfected with a plasmid encoding Factor VIII to treat transgenic mice that are deficient in Factor VIII (page 39, line 10). The specification does not teach how to observe the effect of Factor VIII on vasculogenesis;

however, methods of evaluating the effect of an expressed protein in the host embryo were known in the art at the time of filing (see Ribatti or Downs in 102(b) rejections).

The specification does not enable one of skill to determine what applicants consider a "beneficial" or "detrimental" "test gene product" to vasculogenesis. While the terms beneficial or detrimental were known in the art, the terms are relative and had various meanings in the art. For example, in individuals with a deficiency in Factor VIII, a clotting factor, Factor VIII could be considered beneficial. However, in normal individuals, Factor VIII could be detrimental because overexpression of Factor VIII would cause excess coagulation of the blood. In addition, Factor VIII is not beneficial or detrimental to vasculogenesis because it is a clotting factor and does not effect blood vessel formation. The specification does not teach any "test gene product" that are "detrimental" or "beneficial" to vasculogenesis. Therefore, the specification does not enable one of skill in the art at the time of filing to determine which "test gene products" are "beneficial" or "detrimental" to vasculogenesis as claimed.

The claims encompass making a transgenic allantois by histoincompatible or xenogeneic transplantation; however, the specification does not provide adequate guidance for one of skill in the art at the time of filing to use a transgenic allantois made by histoincompatible or xenogeneic transplantation. The disclosed method requires functional expression of the "test gene product" and for the protein to be functionally expressed, the transplant cannot be under attack by the host immune system. Functional gene expression in a transplant requires the host be histocompatible so as to avoid an attack by the host immune response. Therefore, for the method claimed to be of

use, the effect of an expressed protein on vasculogenesis can only be observed if the host is histocompatible, allogeneic or syngeneic.

The specification does not provide adequate guidance for one of skill to evaluate the effect of a "test gene product" on vasculogenesis. As an example, a transgenic allantois expressing FGF-2 may be transplanted into a histocompatible host allantois and vasculogenesis observed; however, the effect of the "test gene product" on vasculogenesis cannot be evaluated without a comparison to a control for normal vasculogenesis. In fact, FGF-2 may interfere with vasculogenesis because it would cause increased vascularization. Applicants do not provide any methods for one of skill to evaluate whether observed results are expected or unexpected, provide any methods for comparing observed results to a control or to determine the effect of the "test gene product" on vasculogenesis. Without such guidance, it would have required one of skill in the art at the time the invention was made to evaluate the effect of any "test gene product" on vasculogenesis as broadly claimed.

Therefore, in view of the lack of guidance in the specification regarding how to evaluate the effect of a "test gene product" on vasculogenesis, use the method claimed when the transgenic allantois is made using histoincompatible tissues and how to determine whether a test gene product is "beneficial" or "detrimental" to vasculogenesis, the state of the art, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite because it is unclear whether the mesenchymal cells obtained in step a) are transplanted into a host animal in step b) or whether the mesenchymal cells obtained and the transgenic allantois formed are both obtained at the same time by making a transgenic animal. In other words, it is unclear if steps a) and b) are two separate steps or if they occur simultaneously.

Claim 21 is indefinite because the body of the claim does not result in evaluating the observed effect as in the preamble of the claim. Claim 21 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: evaluating the observed effect.

Claim 22 and 23 are indefinite because it is unclear if the limitation is further describing the "test gene product" that was pre-determined to be "beneficial" or "detrimental" or if it is describing a step in evaluating the effect of the test gene product on vasculogenesis to determine whether it is "beneficial" or "detrimental". The purpose of the method claimed is to determine the effect of the "test gene product" on vasculogenesis, so it would be redundant to determine the effect of a "test gene product" that is already known to be "beneficial" or "detrimental" to vasculogenesis. The specification does not teach what applicants consider test gene products that

are "beneficial" or "detrimental" to vasculogenesis. For example, the specification discloses the "test gene product" of LacZ; however, it cannot be determined if applicants consider LacZ a "beneficial" "test gene product, a "detrimental" "test gene product" or some other type of "test gene product". Therefore, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Ribatti (Ribatti et al., 1997, J. Vasc. Res., Vol. 34, pages 455-463).

Ribatti teaches obtaining endothelial cells transfected with a plasmid encoding FGF-2, transplanting the cells into an allantoic membrane and observing the effect of the cells on vascularization (page 456, col. 1, 7 lines from the bottom; col. 2, line 9; page 457, col. 1, line 5; page 459, col. 2, last paragraph through page 460, col. 2, line 5). Endothelial cells are considered mesenchymal cells as claimed because endothelial cells are derived from the mesenchyme. The allantoic membrane transplanted with the transfected endothelial cells is equivalent to the transgenic allantois claimed because the allantoic membrane is part of the allantois. The limitations of whether the test gene product is "beneficial" or "detrimental" to vasculogenesis as in

claims 22 and 23, respectively, is anticipated by Ribatti because Ribatti evaluated whether the expression of FGF-2 was "beneficial" or "detrimental", because the product may be beneficial, detrimental or have no effect and because FGF-2 is beneficial to vasculogenesis. The limitation of "evaluating the effect of a test gene product on vasculogenesis" is an intended use and does not bear patentable weight because it may not occur. Thus, Ribatti anticipates the claims.

6. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Downs (Downs et al., July 1997, Development, Vol. 124, pages 2769-2780).

Downs teaches obtaining allantois expressing lacZ from transgenic mice, transplanting the transgenic allantois into a host allantois and observing the vasculogenesis in the host allantois (page 2770, col. 1, 2 lines from the bottom; col. 2, 1st and 2nd full paragraphs; page 2774, col. 2, line 6 and last line; page 2779, "Umbilical vasculogenesis"). The mesenchymal cells are defined as cells which are part of embryonic mesoderm, consisting of loosely packed, unspecialized cells set in a gelatinous ground substance, from which connective tissue, bone, cartilage and circulatory and lymphatic systems develop (www.dictionary.com, enter "mesenchymal"). Allantoic mesoderm cells inherently become connective tissue, bone, cartilage and circulatory and lymphatic systems. Therefore, the transgenic allantoic mesoderm taught by Downs (page 2774, col. 2, line 6) is equivalent to the transgenic allantois comprising the "mesenchymal cells" claimed because it is equivalent to the transfected allantois taught in the specification and because transgenic allantoic mesoderm inherently comprises mesenchymal cell. The limitations a "test gene product" that is "beneficial" or "detrimental" to vasculogenesis as in claims 22 and 23, respectively, does

not bear patentable weight because it is not clear whether applicants consider LacZ a "beneficial" product, a "detrimental" product or some other type of product and because the product may not be "beneficial" or "detrimental" to vasculogenesis in the method claimed (see 112/2nd). The limitation of "evaluating the effect of a test gene product on vasculogenesis" is an intended use and does not bear patentable weight because it may not occur. Therefore, Downs anticipates the claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

AU 1633
MICHAEL C. WILSON
PATENT EXAMINER